Claims 22-57 stand rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Claims 22-57 stand rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 22-57 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 5,240,711 (Hille et al.) by itself or in combination with U.S. 5,246,705 (Venkatraman et al.) or U.S. 4,466,953 (Keith et al.).

Rejection of Claims 22-57 Under U.S.C. 112, First Paragraph

Claims 22-57 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the application was filed, had possession of the claimed invention. Specifically, Examiner states that the (1) elasticity and the terms (2) "redetachable protective layer" (Claims 22 and 57), (3) "warp threads" (Claims 51 and 53), and "weft threads" (Claims 52 and 53) are not described in a sufficient manner to enable one skilled in the art to practice the invention. Examiner further states that the phrase (4) "obtainable by the reaction of starting material" (Claim 38) is non-enabling as there is no disclosure of the nature of the reaction in order to obtain the claimed material.

Claim 51 has been deleted and replaced with new claim 66 to better clarify the invention. At page 7, lines 19-25, the specification describes the number of warp threads

and weft threads to be used if a woven fabric is used for the backing layer of the transdermal therapeutic system. Warp threads are in the range of 300-350 and weft threads are in the range of 100-140, both measured per 10 cm of unextended fabric.

Applicant respectfully submits that warp threads are threads stretched lengthwise in a loom, which are crossed by weft threads. Weft threads are threads crossing from side to side of the loom to create a web by being interwoven with the warp threads. Applicant respectfully submits that it is known in the art that such threads are related to fabrics which could be used for the backing layer of the present invention. There are numerous references regarding warp and weft. See for example "Winding and Calculating the Warp and Weft" at http://www.asarian-host.org/beaumond/calcul.htm. New claim 66 has been added to better clarify this. Claims 52 and 53 depend therefrom and so Applicant respectfully requests that these rejections be withdrawn.

Claims 22 and 57 have been amended to better clarify the invention. Applicant submits that it would be more accurate to replace the term "redetachable" with the term "detachable." Applicant submits that the term "redetachable" was inappropriately used during the translation of the application from German. The protective layer of the present invention should be removed prior to application and it is not intended that it be replaced if removed from the patient. Because the protective layer is designed to be removable or detachable, the term "detachable" would be more appropriate. Applicant respectfully requests that these rejections be withdrawn.

Elastic deformability is a term that is widely known in the art and is defined in the art as the property of a solid object to be reversibly deformed upon external stress.

Elasticity is understood in the art to mean the elongation of an object due to tensile strength. It is also known as the modulus of elasticity; see Handbook of Plastics, Simonds et al., D. Van Nostrand Company, Inc., 2nd ed., Table 2.8; Mechanics of Materials, Popov, Prentice-Hall, Inc., pp. 29-30. The elasticity coefficient is the elongation an object having a length of 1 meter and a diameter of $1mm^2$ will have due to tensile stress of 1 kg. In this context, Applicant respectfully submits that the term "elasticity of at least 20%" would be understood by those skilled in the art as being elastic to an extent that the elastic backing layer can be reversibly elongated to a length exceeding 20% of its initial length and that reference to "20%" is relative to the initial length, which is set at "100%".

In the specification at page 4, paragraph 3, it is disclosed that the elasticity is determined according to Deutsche Industrie-Norm (DIN) measurements which are the German Industrial Standards and well known in the art and readily available to the public. It is disclosed that the elasticity is determined according to DIN 60 000 and 61 632. By this reference, Applicant respectfully submits that the measurement of elasticity as disclosed would enable one skilled in the art to make and/or use the invention. Thus Applicant respectfully requests that the rejection be withdrawn.

Examiner contends that in claim 38, the term "obtainable by the reaction of starting material" is non-enabling, as there is no disclosure of the nature of the reaction in order to obtain the claimed material. Applicant respectfully submits claim 38 specifies the starting material as well as the product to be obtained, which is namely a polyterephthalic acid diol ester. Applicant submits that this information is sufficient to

enable one skilled in the art to understand the nature of the reaction to be employed and obtain the claimed material. Thus, applicant respectfully submits that claim 38 is enabling for one skilled in the art and so the rejection should be withdrawn.

As amended, claims 22-57 meet the requirements of 35 U.S.C. 112, first paragraph. Therefore, it is respectfully submitted that the rejection under 35 U.S.C. 112, first paragraph be withdrawn.

Rejection of Claim 22-57 under 35 U.S.C. 112, Second Paragraph

Claims 22-57 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, Examiner rejects Claims 22-57 because the expression "elasticity of at least 20%" is allegedly unclear as to the percentage of what; claims 32 and 33 because it is unclear as to what is meant by "microbially nondegradable"; claim 38 as it contains an improper Markush group; claim 50 as one is unsure what is meant by the term "areal proportion"; and claims 51-53 as one is unsure what is meant by "warp thread" and "weft thread".

Regarding the claims pertaining to the elasticity of the backing layer of the claims in their present form, applicant respectfully submits that for the reasons set forth above, claims 22-57, which refer to the elasticity of the backing layer, are clear and meet the requirements of 35 U.S.C. 112, second paragraph. Thus, applicant submits that they particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Regarding claims 32 and 33 which refer to the backing layer being "microbially nondegradable", applicant respectfully submits that the claims are clear and comply with 35 U.S.C. 112, second paragraph as presented. Applicant refers Examiner to the substitute specification at the last paragraph of page 6 which continues onto page 7. Applicant explained that a vivid microbial ecosystem comprising microbes, such as bacteria, fungi, spores, etc., will rapidly develop underneath the transdermal therapeutic system after prolonged use. It is explained in the specification that the preferred materials for the backing layer should not be degradable by any microbes present on the skin and under the transdermal therapeutic system. Any type of degradation, even partial degradation, would severely interfere with the desired properties of the inventive backing layer, namely the elasticity, the water vapour permeability and porosity. Applicant respectfully submits that these claims comply with 35 U.S.C. 112, second paragraph thus requests that the rejection should be withdrawn.

Claim 38 has been amended so that it contains proper Markush group format. Applicant respectfully submits that this rejection be withdrawn.

Claim 50 has been deleted and replaced by new claim 65 to better clarify what is intended to be the invention. Examiner states that it is unclear as to what the term "areal proportion" refers. Applicant respectfully refers Examiner to the substitute specification at page 8, paragraph beginning with "Where woven or nonwoven...", where areal proportion is explained. Applicant submits that areal proportion is related to the woven or non-woven fabric or porous films employed as material for the inventive backing layer of the transdermal therapeutic system. Areal proportion further defines the total area of

all pores present in the fabric, each of which covers an area of at least 400 μm^2. The total area of all pores is set in relation to the size of the sheet of fabric or film employed. Thus, the total area of all pores is a proportion of the area of the sheet.

Applicant further submits that, although not literally given, it would be evident to a person skilled in the art, particularly from the substitute specification at page 8, full paragraph 2, and in Example 1, that the material of the backing layer is a fabric or porous film. Thus, it would be evident that porosity is related to the backing layer rather than to the reservoir layer or detachable protective layer, or even the entire transdermal therapeutic system. Claim 50 has been deleted and replaced to evidence this and now refers back to claim 34 rather than claim 22. As such, Applicant respectfully submits that claim 50 complies with 35 U.S.C. 112, second paragraph and so the rejection should be withdrawn.

Rejection of Claims 22-57 under 35 U.S.C. 103(a)

Claims 22-57 have been rejected as being unpatentable over U.S. 5,240,711 (Hille et al.) by itself or in combination with U.S. 5,246,705 (Venkatraman et al.) or U.S. 4,466,953 (Keith et al.). It is respectfully submitted that these claims in their present form are patentably distinct from the prior art.

Referring to Hille '711, the reference discloses a transdermal therapeutic system for controlled release of buprenorphine. Hille '711does not teach, nor suggest, the use of a backing layer having a longitudinal elasticity, according to the present invention. Specifically, Hille '711, at column 3, line 10, teaches that the backing layer may consist

of flexible or inflexible material and that metal foils alone or coated with a polymeric substrate are used. Although metal foils may be flexible, they do not have a longitudinal elasticity of at least 20%, as it stated in the present invention.

Hille '711 also discloses at column 3, line 14 that fabrics may also be employed as the backing layer. However, Hille '711 does not teach nor suggest that the fabric must, or even could, have a longitudinal elasticity. At lines 14-16, it is taught that the aforementioned fabrics may be used if the components of the reservoir cannot penetrate the fabric due to their physical properties. This teaches away from the present invention since a suitable fabric must be tightly woven, which is in direct conflict with the present invention which provides for unidirectional elasticity.

Examiner contends that there are no superior nor unexpected results that are established showing the criticality of the claimed elasticity, or in particular, the material used. Referring to second comparative example of the specification, a transdermal therapeutic system according to Hille '711 will possess the same wearing comfort as the patch in the comparative example. As disclosed in the specification, one of the objects of the present invention is to provide a patch having tremendously improved wearing comfort. This is a superior result and is not made obvious by the prior art, alone or in combination.

Referring to Venkatraman et al. '705, the reference discloses a transdermal drug delivery system comprising a backing layer made of an elastomeric polymer and having a defined vapor transmission rate and a defined Young's modulus of about 10^4 to 10^9 dynes/cm^2. The present applicant in the specification at page 2 discussed Venkatraman et

al. '705, paragraph 2. The elastomeric polymer of the present invention is preferably an A-B-A block copolymer of styrene (A) and saturated hydrocarbon polymers (B). However, the backing layer of Venkatraman et al. '705 employs a single homogenous sheet of an elastomeric material (Col. 2, lines 17-18). A transdermal therapeutic system according to Venkatraman et al. '705, having a backing layer as described, worn on the skin for a prolonged period will undoubtedly cause the sensation of a foreign body. Therefore, it would not be obvious or apparent to one skilled in the art to apply the system taught in Venkatraman et al. '705 to the present invention.

Referring to Keith et al. '953, the reference discloses the use of an occlusive backing layer (col. 6, line 64 through col. 7, line 2). According to Figures 1 and 2, the backing layer 10 comprises a laminate made of a polyester layer 20, an intermediate metal foil 22, and an inner layer 24. Use of the metal foil 22 prevents the patch from being elastic. The combination of an occlusive and non-elastic backing layer will definitely lead to the sensation of a foreign body when the patch is worn on the skin. Therefore, it would not be obvious or apparent to one skilled in the art to apply the method taught in Keith et al. '953 to the present invention.

To establish a 35 U.S.C 103(a) *prima facie* case of obviousness, there must be some motivation or suggestion in the references to combine the reference teachings. Hille '711, Keith et al. '953 and Venkatraman et al. '705, separately or in combination, neither teache nor suggest such combination, but each rather suggests a system that teaches away from the present invention. It is therefore respectfully requested that the

application defined in the claims is patentably distinguishable over the art under 35 U.S.C. 103(a).

The problem of wearing comfort of a transdermal therapeutic system was neither addressed in Hille '711, nor in Keith et al. '953. These references would not have been considered by one skilled in the art with the intent to solve the problem of wearing comfort, which the present invention addresses, nor do they provide any motivation to solve the aforementioned problem. Although Venkatraman et al. '705 teaches the use of elastomeric polymers, it is not likely that the problem of wearing comfort would be solved by this reference for the aforementioned reasons. The use of a backing layer comprising a unidirectional elastic material having at least a certain elasticity is neither suggested nor made obvious by Hille '711, nor any of the other references alone or in combination.

For the foregoing reasons, it is respectfully submitted that the present application is in condition for allowance, and such action is earnestly solicited. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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Date: 8/29/01

Sean F. Mellino

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Thomas Hille and Lothar Deuer
Serial No.	:	09/486,266/Conf. No. 3529
Filing Date	:	May 3, 2000
Examiner	:	I. Ghali
Group Art Unit	:	1615
Title	:	Transdermal Therapeutic System Comprising a Reservoir Type Pressure Sensitive Adhesive Layer and a Back Layer with Uni-directional Resilience
Attorney File	:	RO0254US (#90568)

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Commissioner for Patents
Washington D.C., 20231

MARKED UP CLAIMS

22. (Amended) A transdermal therapeutic system comprising a [redetachable] detachable protective layer; a pressure-sensitive adhesive reservoir layer; and a backing layer comprising a unidirectional elastic material having an elasticity of at least 20%.

24. (Amended) The transdermal therapeutic system of claim 22 [which] wherein the system is a patch.

38. (Amended) The transdermal therapeutic system of claim 37 wherein the backing material is a polyterephthalic acid diol ester obtainable by the reaction of a starting material selected from the group consisting of ethylene glycol, 1,4-butanediol, 1,4-dihydroxymethylcyclohexane, terephthalic acid, isophthalic acid, adipic acid, azelaic acid, sebacic acid, dimethyl

terephthalate, demethyl azelate, dimethyl sebacate, bisphenol A diglycidyl ether, n-decane-1, 10-dicarboxylic acid, polyethylene glycol and polybutylene glycol.

44. (Amended) The transdermal therapeutic system of claim 22 wherein the backing layer [which faces] facing [outwards] outwardly has a differentiated marking element.

57. (Amended) A method [or] of producing the transdermal therapeutic system of claim 22 comprising the steps of inserting pressure-sensitive adhesive substance reservoir sections in a sequence in [the] a longitudinal direction into a into a presupplied strip-like laminate comprising a [redetachable] detachable protective layer and a backing layer comprising a unidirectional backing material; separating the backing layer by punching; removing the unwanted cut portion of the backing layers; and separating the protective layer in the space between the active substance reservoir sections.

* * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Marked-Up Substitute Specification Under CFR 1.121(b)(iii)

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to a transdermal therapeutic system, in particular an active substance patch, comprising a [redetachable] detachable protective layer, a pressure-sensitive reservoir layer and a backing layer with or without a coating of pressure-sensitive adhesive. The invention also relates to a process for producing such a transdermal therapeutic system (occasionally abbreviated to TTS below) and to the use thereof.

Description of the Prior Art

A TTS is a skin-applied administration form for active substances for delivery through the skin, and has the appearance of traditional patches. It ought to be distinguished from a topical active substance plaster, for example, a rheumatism plaster or a corn plaster. A TTS of this kind can include one or more active substances which are delivered continuously over a fixed period at a predetermined rate to the site of application. ("Heilman Klaus: Therapeutische Systeme – Konzept und Realisation programmierter Arzneiverabreichung" (Therapeutic systems – Design and implementation of programmed drug administration), 4th edition, 1984, Ferdinand-Enke-Verlag, Stuttgart). The fixed period referred to above is usually 24 hours. For the treatment of chronic disorders, however, it is necessary to administer medicaments for a longer period. It may therefore be appropriate to apply a TTS for a period longer than 24 hours, since this is more likely to result in constant plasma levels.

A typical [such] transdermal therapeutic system in the form of a patch is known from EP-B 0 430 019. It has a backing layer which is impermeable to the active substance, a pressure-sensitive adhesive reservoir layer, and a [redetachable] detachable protective layer. The active-substance-impermeable backing layer can be composed or flexible or inflexible material. [Substances which it is mentioned are used for producing such materials are polymer films or metal foils or else a composite comprising a film which has been coated with aluminum by vapour deposition.] Materials such as polymer films, metal foils, or a composite comprising a film which has been coated with aluminum by vapour deposition may be employed as the backing layer. Where such systems are worn on the skin for a prolonged period, [as is necessary (as mentioned

above) for treating chronic disorders in particular] in particular for treating chronic disorders, the relative rigidity of the TTS causes a pronounced sensation of a foreign body [is perceived] on the skin within a short period of time [, owing to the relative rigidity of the TTS]. This is extremely unpleasant for the user.

Another embodiment of such a TTS is described in US-A 5,246,705. The transdermal system it describes has an elastomeric backing layer having a defined vapour transmission rate in the range from 0.1 to 20 $g/m^2/hr$ and a Young's modulus in the range of about 10^4 to 10^9 $dynes/cm^2$. Particularly, preferred materials for the elastomeric backing layer are, for example, A-B-A block copolymers, the A blocks comprising styrene and the B blocks comprising saturated hydrocarbon polymers such as, for instance, ethylene-butylene copolymers, ethylene-propylene copolymers, and the like. When the transdermal therapeutic systems as per [the said] US-A 5,246,705 are worn on the skin for a prolonged period, it is impossible to avoid the above-described sensation of a foreign body.

US-A 4,780,168 discloses a strip-like wound bandage for sealing wounds, which is fabricated from a woven or non-woven polymer-based material [, the said material] having a planar stretching characteristic in the range from 0.5 to 110 (pounds/inch). Materials of such extensibility are, however, not immediately suitable as materials for backing layers of transdermal therapeutic systems. Either their extensibility is too low, in which case the aforementioned unpleasant foreign-body sensation [described above] is felt when [they] the systems are worn on the skin for a prolonged period, or else they are much too extensible, in which case the production of transdermal therapeutic systems is accompanied by the [so-called] curling effect, which is explained below.

During the production of the laminate from which the individual active substance patches are punched, the material for the backing layer comes under tensile stress and the resulting elastic return force means that, during punching, the opposite ends of the patches are each bent up. [Owing to the reject rate during manufacture, this effect results in high costs, together with unnecessary environmental burden.] Because of the reject rate during the manufacturing process, the curling effect results in high costs, as well as unnecessary environmental burdens.

Aside from the abovementioned disadvantages, a material for the backing layer of a wound bandage is also unsuited to a TTS for other reasons [too], such as the required impermeability to the active substance.

The object of the invention is therefore to provide a transdermal therapeutic system which comprises a [redetachable] detachable protective layer, a pressure-sensitive adhesive reservoir layer and a backing layer with or without a coating of pressure-sensitive adhesive and which avoids the aforementioned disadvantages. In particular, there should be no sensation of a foreign body on the skin in the course of prolonged wearing, even for periods of from several days to about 1 or 2 weeks. Furthermore, the production of the TTS should not be accompanied by the curling effect, [so] thus ensuring rational and inexpensive production.

This object is achieved in accordance with the invention by a transdermal therapeutic system, in particular an active substance patch, [which comprises] comprising a [redetachable] detachable protective layer, a pressure-sensitive adhesive reservoir layer and a backing layer with or without a coating of pressure-sensitive adhesive, the backing

layer being [of] a unidirectionally, especially longitudinally, elastic material having an elasticity of at least 20%.

Preferred embodiments of the TTS of the invention are the subject-matter of the dependent claims.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a plan view of the TTS of the invention according to the present invention.

Fig. 2 is a cross section made through plane II-II of the TTS as shown in Fig. 1.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the invention, the TTS features not only a [redetachable] detachable protective layer and a pressure-sensitive adhesive layer but also a backing layer which, optionally, is [likewise] coated with a pressure-sensitive adhesive and which has a specifically defined unidirectional elasticity. With regard to the TTS of the present invention, the elasticity is determined in accordance with the DIN standards 60 000 and 61 632 (April 1985), which are conventionally used for elasticity tests. Originally, these DIN standards [do in fact apply] applied to ideal bandages; however the horizontal force extension unit used to test the elasticity can [, however,] be employed analogously for other materials as well. In accordance with the invention, the backing layer of the TTS is elastic in only one direction, i.e., in a longitudinal or a transverse direction. Relative to the longitudinal axis of the TTS, the transverse axis is that lying at [right angles] a right angle to it. In a circular TTS, the longitudinal and transverse axis are of course identical

in length. In particular, the backing layer material used in accordance with the invention is unidirectionally longitudinally elastic.

In the other direction, the backing layer is non-elastic. Non-elastic means that no elasticity can be found with testing by hand. In the case of [measurement] measurements in accordance with DIN 61 632 [, then] the elasticity is less that 20%. In accordance wit the invention, therefore, the elasticity in one direction, mainly the elastic direction, is above 20%.

Since the production of the patch involves it being punched out from a laminate, it would also be possible to conceive in principle of the TTS being "unidirectionally" elastic at an angle to the longitudinal direction of the patch. Oblique elasticity of this kind is, however, the result of a superposition of elasticity in the transverse and longitudinal directions.

In the TTS of the present invention, the elasticity of the undirectionally elastic material used for the backing layer is preferably less than 150%. In a more preferred embodiment, the elasticity is in the range from 40% to 70%. The most preferred elasticity for a backing layer material, and, accordingly, that which is most advantageous for the achievement of the object on which the invention is based, lies within the range between 44% and 56%, always measured in accordance with DIN 61 632.

Preferred materials for the unidirectionally elastic backing layer are those which are microbially nondegradable. The material should be more than 90%, preferably more than 99%, microbially nondegradable. The degradability can be measured by conventional methods familiar to the person skilled in the art. Low degradability is particularly important in the case of TTSs which are to be worn on the skin for a

prolonged period. The reason for this is that, owing to the transpiration of the skin, a microclimate in which bacteria, fungi, spores, etc. absolutely thrive develops directly below the section of skin covered by the TTS. Consequently, low microbial degradability, especially in the case of prolonged wearing, is extremely advantageous. The material of the backing layer can be a woven fabric, a nonwoven fabric, or a film. Where the backing layer comprises a polymer, the said polymer is selected advantageously from polyethylene, polypropylene, or polyesters, especially polyalkylene terephthalates.

A number of polymeric materials may be mentioned by way of example for the backing layer. Advantageous polymeric materials which meet the above requirement of low microbial degradability are polyterephthalic diesters obtainable by the reaction of a starting material selected from ethylene glycol, 1,4-butanediol, 1,4-dihydroxymethycyclohexane, terephthalic acid, isophthalic acid, adipic acid, azelaic acid, sebacic acid, dimethyl terephthalate, dimethyl azelate, dimethyl sebacate, bisphenol A diglycidyl ether, n-decane-1, 10-dicarboxylic acid, polyethylene glycol and polybutylene glycol.

In the transdermal therapeutic system of the invention, it is likewise possible for a further separating layer to be arranged between the backing layer and the reservoir layer for the purpose, for example, of preventing active substance permeability. In this case, the backing layer on the skin-facing side, and/or the separating layer on the distal side, are/is likewise coated with pressure-sensitive adhesive.

For the effectiveness of a TTS of the invention, it is advantageous for the backing layer to project beyond the reservoir on all sides. This has the advantage that there are no

losses of active substance in the lateral direction. Furthermore, the TTS of the invention can be produced in a particularly inexpensive manner [in this case] since the sections containing active substance can be punched separately. This avoids expensive, environmentally harmful, leftover waste pieces containing active substance. The backing layer of the TTS has a water vapour permeability of at least 0.1 $g/m^2/h$, preferably from 1 to 20 $g/m^2/h$.

Where a woven or nonwoven fabric or else a porous film is used, the porosity lies within the range from 10% to 50%. Porosity here means the proportion of pores having an area of less that or equal to 400 μm^2 as a percentage of the reference area in question. This relative pore area can be determined by measuring and counting the pores of any unextended reference area under the microscope or a thread counter.

If a woven fabric is used for the transdermal therapeutic system (TTS) of the invention, the backing layer has a number of warp threads in the range of 300-350, preferably in the range of 310-330, and/or a number of weft threads in the range from 100 to 140, preferably in the range from 120 to 130, measured in each case per 10 cm of unextended fabric.

The pressure-sensitive adhesive reservoir layer of the transdermal therapeutic system of the invention comprises at least one active substance. This substance is preferably selected from the group consisting of psychopharmaceuticals, analgesics and hormones. Particular substances which may be considered include estradiol as a hormone and buprenorphine as an analgesic. The psychopharmaceutical is preferably a parasympathomimetic. Particularly suitable parasympathomimetics are the following:

1. choline esters, e.g. acetylcholine, bethanechol, carbachol, or methacholine;

2. alkaloids, e.g. arecoline and its derivatives, pilocarpine;
3. choline esterase inhibitors, e.g. demacarium bromide, distigmine bromide, neostigmine, physostigmine, pyridostigmine bromide, galanthamine.

These substances can of course be used in combinations with one another. The active substance content is particularly set [in particular such] so that when the plaster is removed [there is what is known as] a pulloff effect occurs. This effect is explained hereinbelow.

Where a TTS includes a backing layer of limited water vapour permeability, such as a PET film, the skin is unable to give off water vapour at the application site while the TTS is being worn. This water becomes incorported in the skin. At the application site, therefore, the water content is higher than the physiobiological norm. A substance which is difficult for the skin to absorb (such as buprenorphine, for example) becomes incorporated into a deposit in the skin. When the TTS is pulled off, the skin gives off water vapour suddenly. As a result of removal of this water vapour, there is a sudden increase in the concentration of the medicament to above the saturation concentration, since solvent is removed. A stable state is reached by the rapid emptying of the skin deposit. Therefore, as a result of the TTS being pulled off, there is a rapid increase in the plasma concentration of the active substance. The utilization of the pulloff effect is preferred for better utilization of active substance. In accordance with the present invention, therefore, the concentration of the active substance is set such that the abovementioned pulloff effect comes about.

The absolute level of active substance for achieving the pulloff effect cannot generally be defined validly with precision. It varies from one active substance to

another and also depends on the embodiment of the TTS. Setting of the level can, however, be undertaken by the person skilled in the art without undue burden by means of routine experiments. In the case of buprenorphine, the level is about 5-15 % by weight.

The pressure-sensitive adhesive reservoir layer may also include a water-absorbing polymer. In one preferred embodiment, the water-absorbing polymer is a polyvinylpyrrolidone. The polyvinylpyrrolidone preferably has a molecular weight in the range from $1x10^3$ to $2x10^6$. Such polyvinylpyrrolidones include Kollidon®.

For special purposes, moreover, such as for use in hospitals with many patients or for use in double blind studies where TTS containing active substance are compared with placebo TTS, it is preferred for the side of the TTS that faces outwards, that is, away from the skin, to carry in the backing layer a marking/control element which is differentiated from the remaining area.

This element can differ from the remaining portion of the backing layer in its structure or in other properties, such as elasticity or porosity. By means of such a marking/control element the properties of the backing layer can be made different. For example, the elasticity of such an element can be greater than the elasticity of the remaining portion of the backing layer. If such a marking/control element is specifically incorporated in one portion of the backing layer, then its relative elasticity, where desired, is preferably within a range situated about 20% below or about 20% above the elasticity of the remaining portion of the backing layer.

The marking/control element can also serve to distinguish the individual TTSs from one another in terms of their active substance content. This is done preferably by

means of coloured marking, for example by means of a coloured thread or stripe. This is particularly advantageous if the TTS has to be held ready in large quantities at different dosages at one location: for example, a hospital with large numbers of patients.

Because of its backing layer, the [The] transdermal therapeutic system of the invention is particularly suitable for use as a multi-day plaster [owning to its backing layer, which is tailored to this requirement]. The backing layer is tailored to this requirement. Thus it can be used in particular to treat chronic pain or else to treat drug dependency.

The TTS of the present invention is produced by means of conventional processes. In general, such a process comprises the steps of producing the individual TTSs by punching from a presupplied strip-like laminate comprising the unidirectionally elastic backing layer of the invention, an active substance layer and a [redetachable] detachable layer.

In one particularly preferred process for producing the TTS of the invention, the above steps are modified to the effect that, in a presupplied strip-like laminate having an optionally pressure-sensitive adhesive, unidirectionally elastic backing layer and a [redetachable] detachable protective layer, pressure-sensitive adhesive active substance reservoir sections are inserted in sequence in the longitudinal direction, and the backing layer is separated by punching [and then]. Lastly, the protective layer in the spaces between the active substance reservoir sections [the protective layer] is separated. This specific process [has the feature that it] is highly advantageous from both economic and environmental standpoints. Indeed, the separate insertion of the active substance reservoir sections avoids the formation of waste comprising active substance (which is

usually very expensive) and thus the need to dispose, again at a great expense, of such waste. A similar process is described in DE-B 41 10 027, which [in this respect] is expressly incorporated herein by reference.

The invention is elucidated below with reference to a drawing and an exemplary embodiment. [In the figures,

Fig. 1 shows a plan view of the TTS of the invention;

Fig. 2 shows a section made at II-II through the TTS of Fig. 1]

[Fig. 1 shows, diagrammatically,] Referring now to Fig. 1, a plan view of a TTS of the present invention is shown and referred to generally at numeral 10. Lying atop the [redetachable] detachable protective layer [(1)] 12, [which in the present case is rectangular], is the backing layer [(5)] 20, which is coated with a pressure-sensitive adhesive devoid of active substance. For exemplary purposes, detachable protective layer 12 is shown as rectangular. It has the form of a rectangle with rounded corners 24. The punching line [(1a)] 12a outlines the form of the backing layer [(5)] 20. It extends outside the laminate comprising the reservoir [(2)] 14 and, optionally, a barrier or separating layer [(3)] 16. The course of the punching line 12a means that loss of active substance is avoided when the [patch] TTS 10 is punched out. Within the backing layer [(5)] 20 it is possible to make out the contours of the reservoir [(2)] 14 and of the optional barrier or separating layer [(3)] 16.

In the TTS shown, with the unidirectionally elastic backing layer [(5)] 20, the [latter] the backing layer 20 protrudes beyond the abovementioned laminate comprising the reservoir 14 on all sides. The reservoir 14 is preferably rectangular in form. The

rectangular from is preferred since it [enables losses of] prevents active substance loss [to be avoided] when the reservoir is cut.

[Fig. 2 is a cross section through II-II of Fig. 1.] Referring now to Fig. 2, a cross section through plane II-II of Fig. 1 is shown. For clarity, the [thicknesses] thickness of the layers have been exaggerated. The TTS 10 features the reservoir [(2)] 14, the removable protective layer [(1)] 12, [and also] the optional barrier layer [(3)] 16, and a further layer [(4)] 18 of pressure-sensitive adhesive devoid of active substance[,]. [this] This layer [(4)] 18 [being] is necessary when a barrier layer [(3)] 16 is present. In this depicted embodiment, the backing layer [(5)] 20 and the pressure-sensitive adhesive layer [(4)] 18 devoid of active substance protrude beyond the abovementioned laminate on all sides.

Examples

In order to produce the unidirectionally elastic backing layer of the present invention, a woven polyester fabric having the following features was produced by means of the techniques known to the person skilled in the art.

TEST FEATURES	UNIT	Nominal	MIN	MAX	$\bar{X}$
WIDTH OF MATERIAL	mm	1500	1300	1390	1360
BASIS WEIGHT (unextended) (DIN 53854 + DIN 53884)	g/m^2	100	95	103	100
EXTENSION (longitudinal)	%	-	-	-	-
(transverse)	%	50	46	52	48
(DIN 61632)					
NUMBER OF WARP THREADS Per 10 cm unextended		320	310	330	324
NUMBER OF WEFT THREADS Per 10 cm unextended		125	124	126	124

In addition 49.175 kg of Durotak type 387-2054 (48.3% by weight solution), 4.450 kg of melted laevulinic acid, and 6.675 kg of oleyl oleate were homogenized with stirring. Then, 4.450 kg of Kollidon 90F were added in portions. Following dilution with 6.800 kg of ethanol, the mixture was stirred at 170-190 rpm for 5 hours. Then, 4.450 kg of

buprenorphine base, suspended in 4.500 kg of ethyl acetate, [were] was added. The mixture was diluted with 4.500 kg of ethyl acetate.

The mixture was stirred at 170 rpm for about 7 hours. It was then tested for homogeneity. When the composition was homogenous it was devolatilized, with the stirrer switched off.

Following homogenization, the adhesive composition was applied to a siliconized polyester film. The organic solvents were removed by drying at normally 35°C to 80°C. The laminate, comprising siliconized polyester film and buprenorphine-containing pressure-sensitive adhesive layer, was subsequently covered with a second polyester film 23 µm thick.

The siliconized polyester film was removed from the resulting active substance laminate. Subsequently, rectangles measuring 50 cm^2 were punched out and were placed with their adhering face, at intervals of 3 cm, onto the siliconized fave of a further 100 µm polyester protective film. Atop these reservoir sections was placed the unidirectionally elastic, woven polyester fabric, which in this case was likewise coated with pressure-sensitive adhesive. Subsequently, individual longitudinally elastic patches were punched out. A wearing test was conducted on n=10 subjects using this TTS of the invention.

Comparative Example 1

In this example, a bidirectionally elastic woven polyester fabric was used instead of the unidirectionally elastic woven polyester fabric of the invention. The extensibility of this fabric (longitudinal and transverse extension) was 30% as measured in accordance with DIN 61 632. Its basis weight was 109 g/m^2. This material was a polyethylene

terephthalate. In other respects, the TTSs produced in accordance with this comparative example were the same as those of the inventive example.

Using the TTSs according to this comparative example, a wear test was likewise conducted on n=10 subjects.

Comparative Example 2

TTSs were prepared in accordance with Example 1 and Comparative Example1 but using a rigid polyester film (15 μm thick) of Hostaphan® RN 15, Hoechst AG, coated with pressure-sensitive adhesive, instead of a unidirectionally or bidirectionally elastic backing layer, respectively. In this case as well, a wear test was carried out with the resulting TTSs on n=10 subjects.

Evaluation

The comparative wear test of the TTSs of Example 1, Comparative Example 1 and Comparative Example 2 gave the following result[:].

When polyester film was used as the backing layer (Comparative Example 2), a sensation of a foreign body occurred on the very first day. On the second day, creasing occurred and, beginning on the third day, the TTS became detached. The TTS of Example 1 and that of Comparative Example 1 were torn without problems by all 10 subjects, with no sensation of a foreign body, with no impairment of bond strength, and, furthermore, with no skin irritations, for at least seven days. In respect of wear comfort, therefore, the TTS of Example 1 and that of Comparative Example 1 are approximately equal. However, with regard to the production of the TTS of Comparative Example 1, complications in production occurred in a frequency of more than 50%, these complications being attributable predominantly to the curling effect.

Abstract

A transdermal therapeutic system (TTS), in particular a patch, is described, comprising:

-a [redetachable] detachable protective layer

-a pressure-sensitive adhesive reservoir layer and

-a backing layer with or without a coating of pressure-sensitive adhesive and featuring a unidirectionally, preferably longitudinally, elastic material having an elasticity of at least 20%. The TTS is particularly suitable for use as a multi-day plaster, for the treatment, for instance, of pain or of drug dependency.